

REMARKS

Reconsideration and allowance are respectfully requested. Claims 22-30 and 38-41 are pending. Non-elected claims 30 and 39 were withdrawn from consideration by the Examiner.

The aminoadamantanes of formula (IV) have been taken out of claim 22, and a new claim 41 has been added specifying the synergistic combination of the aminoadamantanes and interferon. This is based on original claim 38 and the description (e.g., the specification at page 1, lines 30, to page 2, line 5). A new claim 40 has been added to define substituent Nu by the formulae appearing in the specification at page 13.

Specification/Claim Objections

Claims 22 and 28-29 were objected to as allegedly informal. Applicants traverse.

In claim 22 in formula (I), the substituent "H" is used to denote hydrogen which is well-known in the chemical arts. It should not be necessary to define the term "H" in a claim because one of ordinary skill in the art would readily understand what is meant.

The term "IU" has been inserted into claim 28 as suggested by the Examiner.

The abbreviations "NSC 382046", "NSC 7364", "NSC 302325", "NSC 184692D" and "NSC 382034" used in claim 29 relate to particular chemicals which can be found in the National Cancer Institute (NCI) open database compound collection. Each entry has been assigned a numeric NCI compound identifier called an NSC number. The term "NSC" is derived from the acronym for Cancer Chemotherapy National Service Center (CCNSC). This organization was established at the NCI by congressional authorization in 1955 and was the predecessor of the Developmental Therapeutics Program (DTP). The abbreviations are thus well-known in the art. Furthermore, each of the designations is identified by compound name in the present specification (see Table 1 at pages 14 to 15 and Table 2 at pages 16 to 17). Therefore, the abbreviations objected to stand for specific compounds and their meanings are clear to those of ordinary skill in the art.

Withdrawal of the objections is requested.

35 U.S.C. 112 – Definiteness

Claims 22-29 and 38 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Since the term "metabolite derivatives" has been canceled from claim 22, this portion of the rejection is moot. The term "imidazole derivatives" also appears but, in that case, the derivatives are precisely defined by formula (V').

In formula (I) of claim 22, the exact position of substituent X is defined in the formula. Furthermore, one of ordinary skill in the art would readily understand from that formula how substituent Nu is attached to the ring containing X and would have no difficulty in understanding the location of any of the heteroatoms.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levensgood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Claims 22-29 and 38 were rejected under Section 103(a) as allegedly unpatentable over the combination of Najarian (WO 98/19670) and Sjogren (U.S. Patent 5,380,879). Applicants traverse.

Sjogren discloses the use of derivatives of mycophenolic acid, for example as anti-viral agents. The anti-viral agents are further discussed at column 18, lines 30 to 38, of the '879 patent wherein they are described as being useful in treating specific types of viruses, but treatment of infections by flavivirus or rhabdovirus is not described.

There is no reference in Sjogren to the possible use of mycophenolic acid derivatives in the treatment of such viral infections. In contrast, the present invention relates to a method of treating a host having a flavivirus or rhabdovirus infection by administering a combination of interferon and a further compound, for example a mycophenolic acid compound of formula (II) as defined in present claim 22. Flaviviruses are positive stranded RNA viruses and rhabdoviruses are negative stranded RNA viruses. Such viruses operate quite differently from the retroviruses and herpesviruses described by Sjogren, and one of ordinary skill in the art would not assume that treatments which are disclosed to be effective against retroviruses and herpesviruses would have any effect on the flaviviruses and rhabdoviruses of Applicants' invention. Sjogren therefore neither teaches nor suggests the presently claimed invention.

Najarian discloses a method for treating hepatitis C infection by administration of at least two compounds chosen from nucleoside analogues, quinolone antibiotics, and amantadine anti-viral agents. Dependent claim 7 of WO 98/19670 specifies that the at least two compounds are substantially free of interferon. It is clear from the description of Najarian that interferon can result in serious side effects in the treatment of hepatitis C. In particular, the Examiner is directed to Example 3 where the patient had previously been given an interferon therapeutic agent to treat hepatitis C infection and experienced side effects which are believed to be due to the interferon therapy including depression, headaches, fevers and chills. The interferon therapy was immediately discontinued and the patient was treated with Najarian's combination therapy and it appeared that the side effects disappeared. Although certain of the examples in WO 98/19670 use a combination of interferon with some other agents, it is clear that such a therapy is not always appropriate. Therefore, one of ordinary skill in the art would not be motivated to modify treatment of hepatitis C infection with a combination therapy including interferon.

Claim 22 has been amended to remove references to amantadine agents. New claim 41 specifies that a combination of interferon and an aminoadamantane compound is synergistic. There is no teaching or suggestion in either of the cited references that a combination of interferon and an aminoadamantane compound would have a synergistic effect. This synergistic effect is evident from the results presented in the present application at Table 21. Table 21 at page 41 of the specification reports on the combination therapy of VSV and kunjin virus. The table shows a CI value in the last column. As explained at page 24, line 21, to page 25, line 3, of the specification, two agents have a mutually additive effect when the CI value is equal to 1, but there is a synergistic effect when the CI value is less than 1. The Examiner will see that the CI values shown in Table 21 are all less than 1, confirming a synergistic effect.

As noted above, Sjogren only refers to treatment of retroviruses and herpes-viruses, and this reference would not be considered relevant to the present invention which is concerned with treatment of flavivirus and rhabdovirus infections. There is also no teaching or suggestion in Najarian that the combination of interferon and an anti-viral

agent as defined in present claim 22 could have a synergistic effect. In fact, Najarian would discourage the skilled person from combining interferon with other antibiotics, particularly aminoadamantane, in view of the stated possible side effects.

Therefore, Sjogren and Najarian taken alone or in combination would not suggest the presently claimed invention to one of ordinary skill in the art.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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